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FISCHER INDOLE LIKE SYNTHESIS

AN APPROACH TO THE PREPARATION OF BENZOFURANS AND BENZOTHIOPHENES

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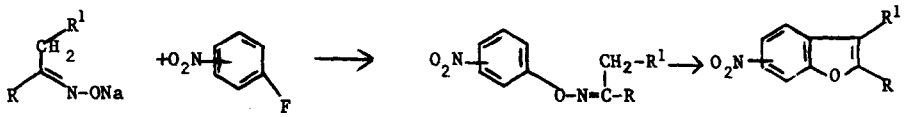
The disclosure by Sheradsky (1) of the application of the Fischer indole synthesis to the preparation of benzofurans prompts us to report our findings in this area.

The low yields reported for the preparation of O-phenylhydroxylamine (2) and its instability caused us to seek a more efficient approach to the preparation of O-phenyloximes. The oxime ethers III were prepared by refluxing the sodio salt of the appropriate oxime I with a fluoronitrobenzene II in tetrahydrofuran or dioxane followed by removal of the solvent and recrystallization of the residue from aqueous ethanol or petroleum ether. Some of the compounds prepared (in 70-96% yields) are: acetone O-(p-nitrophenyl)oxime (IIIa), m.p. 104-105;



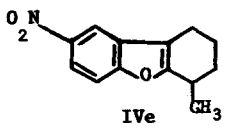
I II III IV

acetone O-(o-nitrophenyl)oxime (IIIb), m.p. 56-57; cyclohexanone O-(p-nitrophenyl)oxime (IIIc), m.p. 100-102; cyclohexanone O-(o-nitrophenyl)oxime (IIId), m.p. 49-51; 2-methylcyclohexanone O-(p-nitrophenyl)oxime (IIIe), m.p. 77-79.

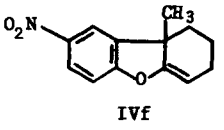
Cyclizations were effected by refluxing with conc. hydrochloric acid in absolute ethanol.

Compounds prepared from the corresponding oxime ethers (in 65-100% crude yields) are: 2-methyl-5-nitrobenzofuran (IVa), m.p. 97-98 (reported (3), m.p. 97°); 2-methyl-7-nitrobenzofuran (IVb), m.p. 101-102; 1,2,3,4-tetrahydro-8-nitrodibenzofuran (IVc), m.p. 148-149; 1,2,3,4-tetrahydro-6-nitrodibenzofuran (IVd), m.p. 103-104; 1,2,3,4-tetrahydro-1-methyl-8-nitrodibenzofuran (IVe), m.p. 101-103.

Cyclization of the 2-methylcyclohexanone oxime ether IIIe gave a near quantitative yield of the benzofuran IVe, with no evidence of the isomeric IVf.



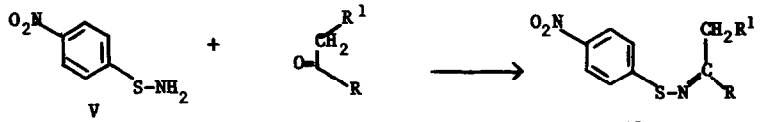
IVe



IVf

By contrast, the normal product in the indole series, 1-methyltetrahydrocarbazole is obtained in minor yield along with the isomeric 11-methyltetrahydrocarbazolenine as the major product (4,5).

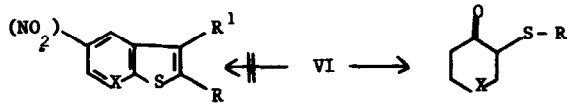
Extending the work to the preparation of benzothiophenes involved the reaction of a sulfenamide of type V with an appropriate carbonyl compound in benzene, toluene or xylene with azeotropic removal of water to give the desired intermediates VI in greater than 90% yield.



V VI

Cyclohexanone with p-nitrobenzenesulfenamide (V) (6) yielded N-cyclohexylidene-p-nitrobenzenesulfenamide [VIa, R,R^1= $-(CH_2)_4-$], m.p. 82-84 . Analogously, 2-pyridylsulfenamide (7) with cyclohexanone yielded N-cyclohexylidene-2-pyridyl-sulfenamide (VII), m.p. 56-58°. With N-methyl-4-piperidone, 2-pyridylsulfenamide gave N-(1-methyl-4-piperidylidene)-2-pyridyl-sulfenamide (VIII), a viscous oil which was not purified but was homogenous by T.L.C.

Attempted cyclizations utilizing the same conditions as for the benzofurans did not result in the formation of benzothiophenes X.



X IX

a. X = C

b. X = N

a. R = p-nitrophenyl
   X = CH_2

b. R = 2-pyridyl
   X = $-N-$
   CH_3

Compound VIa gave a 50-70% yield of p-nitrophenyl disulfide and 15-30% of 2-(p-nitrophenylthio)-

cyclohexanone (IXa), m.p. 94-96°. With compound VIII, a 60% yield of 1-methyl-3-(2-pyridylthio)-4-piperidone (IXb), m.p. 74-76° was obtained.

The mechanism of this rearrangement is presently under investigation. All compounds had analyses and spectra (I.R., U.V. and N.M.R.) consistent with assigned structures.

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